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Pharmaceuticals Inc.

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

August 26, 1999

Docket No. 99D-0529, Draft Guidance for Industry on Changes to an Approved NDA or ANDA

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Dear Sir or Madam:

Boehringer Ingelheim Pharmaceuticals, Inc. wishes to provide the following general and specific comments on the subject draft Guidance for Industry. For convenience, our specific comments are referenced to the sections and lines numbers of the draft Guidance.

General Comments

1. Where applicable, the ICH Guidelines should be referenced, and care should be taken to ensure consistency between this Guidance and the concepts/terminology of the ICH Guidelines. For example, we recommend that the Guidance apply the definition and terminology for "impurities" as defined in the ICH Guidelines Q3A[1] and Q3B[2]. In a number of places, the draft Guidance refers to "impurities and degradation products". Since according to the ICH Guidelines, degradation products are a subset of "impurities", we suggest that the draft Guidance use terms such as "organic impurities", or "synthetic impurities and degradation products", as appropriate, to be consistent with ICH definitions.

   As another example, the definition of "specification" should be fully consistent with, and referenced to ICH Q6A[3].

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[1] ICH Q3A Guideline for Industry, Impurities in New Drug Substances

[2] ICH Q3B Guideline for Industry, Impurities in New Drug Products

[3] ICH Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

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2. The Guidance defines (**Line 26**) and uses the word "potency" throughout the document to mean "e.g., biological activity, bioavailability, bioequivalence". Although we believe that "potency" is correctly used in the context of "biological activity", it appears inappropriate to use this word to mean "bioequivalence/bioavailability". We suggest the term "*in vivo* performance" in place of the word "potency" as used in this Guidance.

3. We appreciate the Agency's efforts in giving examples of changes that could be submitted in the Supplement categories and Annual Report. However, we find many of the examples to be confusing and contradictory. For example, in Section 6, which deals with major site changes requiring a Prior Approval Supplement, Example 4 in **Lines 262- 269** is a move to a site on a different campus for a modified release solid oral dosage form. However, Example 6 in **Lines 277 – 279** appears to provide an exception for a move to a site on a different campus for modified release solid oral dosage forms.

4. Many of the specific comments offered in the following part of our letter concern changes for drug substance. Although we wish to provide these individual comments, we recommend that drug substance changes be deleted from this Guidance, and that reference be given to FDA's BACPAC I and BACPAC II Guidances.

Specific Comments

Section II. REPORTING CATEGORIES
- **Lines 57 – 73**

It would be helpful for the Guidance to provide more detail to assist NDA/ANDA holders distinguish between moderate changes that may be reported as a ***Supplement-Changes Being Effected in 30 Days*** and a ***Supplement-Changes Being Effected***.

Section IV. ASSESSING THE EFFECT OF MANUFACTURING CHANGES
- **Lines 105 – 111**

We object to use of the word "validate" as defined in this draft Guidance. "Validation" is a word widely used and understood by regulators and the pharmaceutical industry in the context of manufacturing validation and analytical validation. Although FDA has provided a footnote to explain how the word is used in the context of this draft Guidance, we believe that there is a high potential for confusion in using "validate" to mean "assess the effects of a manufacturing change". We recommend that the word "validate" in these lines be changed to "evaluate".

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Section VI. SITES

We recommend that a glossary definition be provided for the words "site" and "facility". The meaning of these words in this Guidance is not clear.

For example, in **Lines 248 – 252**, the two words appear to be used as synonyms, *i.e.*, "*A move to any site.....when the new facility has never been inspected by FDA....*"

In **Lines 271 – 276**, the words suggest site is a location within a facility, *i.e.*, "*Transfer of manufacturing ...to a...different aseptic processing facility. Once this change has been approved, subsequent site changes to the facility for similar products....*"

Lines 288 – 291 suggest a site may be a building or a room, *i.e.*, "*A move to a site on the same campus (e.g., building changes) or within a single facility (e.g., room changes)....*"

We appreciate that these words "site" and "facility" are also used in other FDA Guidelines (e.g., the SUPAC Guidelines). It would be very helpful for a definition of these words to be available to industry.

- **Lines 256 - 261**

The third example given of a major change is a move to a new site where there is also a change in the synthesis of a drug substance. FDA's BACPAC I Guidance deals with changes of the synthesis up to and including the step that produces the final intermediate. As acknowledged in BACPAC I, the category of "manufacturing process changes" may encompass a wide range of process-related changes. It is inappropriate to categorize as "major", all site changes involving a change in the route of synthesis of the drug substance. Per PACPAC I, many synthetic process changes are appropriately classified as "moderate". Example 3 should be revised either to qualify the statement on drug substance synthesis changes, or alternatively, remove mention of drug substance synthesis changes and refer to BACPAC I/II.

- **Lines 294 – 300**

Under FDA's PAC-ATLS Guidance, a change in a testing facility is a ***CBE-30 days***, provided the conditions given on Lines 295 – 300 are met. It does not seem necessary to include the qualifier "on a different campus" in this example.

Section VII. MANUFACTURING PROCESS

- **Line 413**

We do not agree that a change from filtration to centrifugation should necessarily be considered a major change. This change is frequently done in chemical production. With the understanding that the change should be appropriately validated, if an assessment of the change shows no adverse impact on the quality of the drug substance, this change should be classified as a minor change.

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Lines 414 - 420
The examples in these two lines appear to be inconsistent with BACPAC I and also inherently contradictory. Per FDA's BACPAC I Guidance, a synthesis process change may be categorized as "major" or "moderate" depending on the nature of the change up to and including the final intermediate. Therefore, it is inappropriate to classify all change in the route of synthesis as "major". Furthermore, since BACPAC II has not yet been issued, it is unknown whether or not all process changes after the final intermediate will be classified as "major". We suggest that both lines 414 and 416 be deleted.

- **Lines 466 - 467**

BACPAC I does not address a change to redefine the final intermediate as a starting material. Since BACPAC II has not yet been issued, it seems premature to exclude the final intermediate from being considered a moderate change in reclassifying the starting material.

Section VIII. SPECIFICATIONS

- **Lines 517 – 520**

The examples given in these lines should be qualified as being applicable to drug substance, but not to intermediates in the synthesis. Such changes in specifications should be classified as "moderate" for the final intermediate, and as "minor" for penultimate intermediates.

Section XI. MISCELLANEOUS CHANGES
Lines 782 – 783
We do not agree that all changes to an approved stability protocol should be considered "major". Certain changes to an approved stability protocol should be appropriately classified as "moderate" or "minor", e.g., the addition of a specification or change in an analytical method to provide increased assurance of drug product quality over shelf life.

In closing, we wish to thank FDA for the opportunity to comment on this new draft Guidance. Although we believe that substantial revision is needed, we see this draft Guidance as an important advance to the regulatory management of changes to approved applications. Given the importance of the topic, we encourage FDA to continue dialogue with the pharmaceutical industry on this Guidance. We request that a revised draft Guidance be published to allow further public comment.

Please contact the undersigned with any questions or comments on this correspondence.

Sincerely,

Patricia Watson

Patricia Watson
DRA Technical Director
Drug Regulatory Affairs

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